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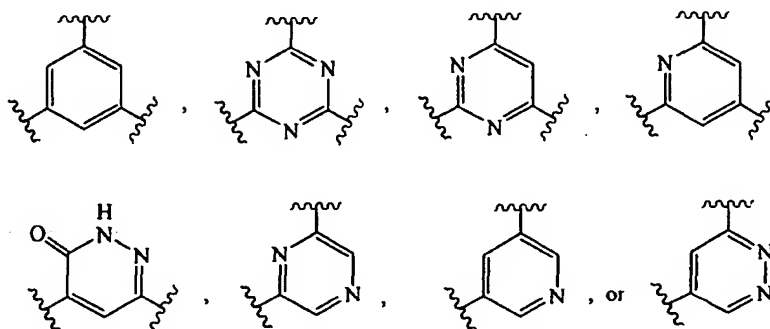
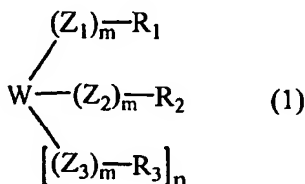
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(54) Title: CERTAIN AROMATIC MONOCYCLES AS KINASE MODULATORS



(57) Abstract: Compound having Formula (I): wherein (W) is a monocyclic ring having the structure are useful as modulators of kinase activity.

CERTAIN AROMATIC MONOCYCLES AS KINASE MODULATORS

BACKGROUND

[0001] This invention relates to benzenes, pyridines, pyrimidines, pyrazines, pyridazines, triazines, and related compounds, which, when appropriately substituted, are modulators of kinase activity. This invention also relates to pharmaceutical compositions comprising such compounds, and to the use of such compounds in treating a variety of kinase-associated disorders. Additionally, this invention relates to the use of such compounds as probes for the identification of kinases of therapeutic interest.

[0002] One of the central post-translational control elements in eukaryotic signal transduction is the phosphorylation of the hydroxyl moiety of serine, threonine, or tyrosine. The phosphorylation state of a given protein can govern its enzyme activity, stability, protein-protein binding interactions, and cellular distribution. Phosphorylation and dephosphorylation is thus a "chemical switch", which allows the cell to transmit signals from the plasma membrane to the nucleus and to ultimately control gene expression. Although the exact mechanisms of signal transduction have yet to be elucidated, kinases are involved in the control of cell metabolism, growth, differentiation, and apoptosis. These signaling mechanisms affect the onset of cancer, metabolic disorders (for example diabetes), inflammation, immune system disorders, and neurodegeneration. Certain kinases have been implicated in cell proliferation and carcinogenesis. For example, many human cancers are caused by dysregulation of a normal protein (e.g., when a proto-oncogene is converted to an oncogene through a gene translocation). Because kinases are key regulators they are ideal drug design targets.

[0003] Inhibitors of kinases are among the most important pharmaceutical compounds known. Tyrosine kinase inhibitors are useful in inhibiting T-cell proliferation, and thus they are useful as immunosuppressive agents for the prevention or treatment of graft rejection following transplant surgery and for the prevention or

treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis. Other tyrosine kinase inhibitors have been described, for example, in U.S. Patent No. 5,593,997 to Dow et al. Erlotinib (CP-358774) is a quinazoline derivative under development as an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor for treatment of solid tumors including non-small cell lung cancer (NSCLC), pancreatic cancer, breast cancer, and neck cancer. In addition, AstraZeneca is developing gefitinib (ZD-1839; Iressa), an inhibitor of epidermal growth factor receptor 1 (EGFR1) tyrosine kinase, for the potential treatment of cancers which over-express EGF receptors, including non-small cell lung cancer (NSCLC) and other solid tumors such as breast tumors. Gleevec and Imatinib (STI-571), from Novartis, are tyrosine kinase inhibitors indicated for treatment of chronic myelogenous leukemia (CML), prostate tumors, and gastrointestinal stromal tumors, among others. CEP-1347 (Cephalon Inc.) is an indolcarbazole choline acetyltransferase inhibitor and c-jun N-terminal kinase inhibitor for treatment of Alzheimer's disease, Parkinson's disease, and AIDS-related peripheral neuropathy. Cephalon is also developing CEP-701, an orally active tyrosine kinase inhibitor for the potential treatment of prostate and other cancers. A PDGF receptor tyrosine kinase inhibitor (SU-101, leflunomide) is being investigated for treatment of various cancers and rheumatoid arthritis. Sugen has also investigated the anti-cancer effects of the FLK-1 tyrosine kinase inhibitor Semaxanib, particularly for colorectal and lung cancers, leukemia, Kaposi's sarcoma, and others.

[0004] Serine/threonine kinase inhibitors are also pharmaceutically important. Eli Lilly is developing LY333531 (ruboxistaurin), an inhibitor of protein kinase C beta, for treatment of diabetic macular edema and diabetic retinopathy. Flavopiridol (Aventis) is a synthetic flavonoid inhibitor of cyclin-dependent kinases, is under development for treatment of mantle cell lymphoma (MCL) and fludar refractory chronic lymphocytic leukemia (CLL). One Raf kinase inhibitor (BAY-43-9006, Bayer) is in development for treatment of solid tumors and myeloid leukemia, and another (ISIS 5132, Isis) is being investigated for treatment of ovarian cancer. Several p38 mitogen-activated protein kinase inhibitors (VX-745, VX-702, and VX-850, Vertex, and SCIO-469, Scios) have been investigated for treatment of inflammation, rheumatoid arthritis, and myelodysplastic syndrome (MDS).

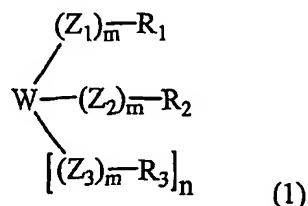
[0005] Highly selective, cell-permeable modulators of one or more individual kinases would thus be useful in the treatment of various kinase-implicated disorders. Such compounds would also be useful for the systematic investigation of the cellular function of one or more kinases, and thus, would provide invaluable tools for the identification of various kinases of therapeutic interest.

The compounds of the present invention belong to the family of nitrogen-substituted substituted monocycles. Other related substituted aza-monocycles have been reported to be useful as antiviral agents (see, for example, WO 01/22938), as fungicides (see, for example, EP 0 503 436), as anti-prion agents (see, for example, WO 02/93164), and as Corticotropin-Releasing Factor (CRF) receptor inhibitors (see, for example, WO 02/096421, WO 01/60806, and WO 96/39400). Activity against kinases has also been reported (see, for example, Gleevac, as well as EP 0 564 409, US 5,521,184, WO 02/04429 and WO 01/25220). Certain examples have been reported as sorbitol dehydrogenase inhibitors, as well as claimed for treatment of complications resulting from diabetes (see, for example, WO 00/59510, and also US 5,728,704; US 5,866,578; US 5,138,058 and US 5,215,990). Other aromatic monocycles have been reported to be useful as UV stabilizers (see, for example, EP 775 698). In addition, other aromatic monocycles have been reported as useful in treating IMPDH mediated diseases, such as transplant rejection and autoimmune diseases (see, for example WO 00/25780).

[0006] At least one process patent for the synthesis of substituted triazines has been filed (see, for example, WO 81/03020).

SUMMARY

[0007] In one embodiment, this invention is directed to a composition comprising a compound of Formula 1:



a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein

[0008] one or two of R₁, R₂, and R₃ may each independently be hydrogen; straight or branched chain (C₁-C₇)alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl ring; (cyclo(C₃-C₆)alkyl)methyl; (C₁-C₆)alkoxy; (C₁-C₆)alkyloxy(C₁-C₆)alkoxy; or sulfonamide, and

[0009] R₁, R₂, and R₃ may each independently be

mono- or di((C₁-C₆)alkyl)amino, wherein the alkyl group may be unsubstituted, mono- di-, or tri-substituted with phenyl, (C₁-C₇)alkoxy or phenoxy, further wherein the phenyl and/or phenoxy may be unsubstituted or substituted with hydroxy, nitro, cyano, amino, halogen, straight or branched chain (C₁-C₇)alkyl or (C₁-C₆)alkoxy;

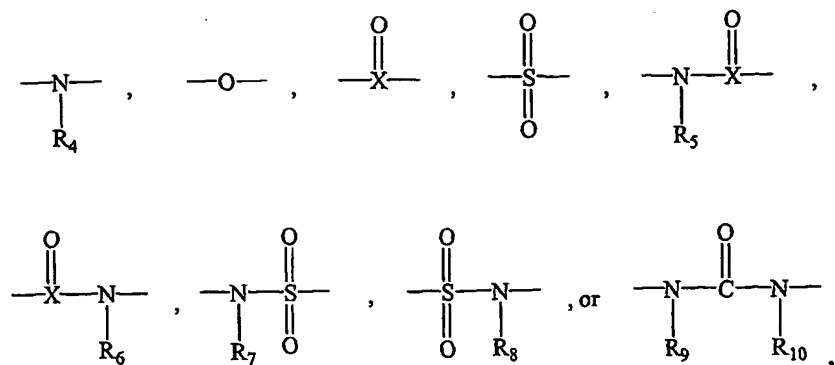
phenyl, benzyl, or heteroaryl which may be unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, acetyl, phenyl which may be unsubstituted or substituted with one or more of (C₁-C₇)alkyl, (C₁-C₇)alkoxy, hydroxy, nitro, oxo, cyano, amino, or halogen, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, mono- or di((C₁-C₆)alkyl)amino(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkyl which may be unsubstituted or substituted with one or more of hydroxy, nitro, oxo, cyano, amino, or halogen, or heteroaryl which may be bonded through an ether, sulfide, or oxo group;

heteroaryloxy or phenoxyphenyl where each heteroaryl or phenyl may be independently unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, or amino(C₁-C₆)alkyl;

4-phenyl- or 4-heteroaryl-1-piperazinyl where the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, mono- or di((C₁-C₆)alkyl)amino(C₁-C₆)alkyl);

[0010] n is 0 or 1;

[0011] Z₁, Z₂ and Z₃ are each independently



wherein

X is C or S; and

R_4-R_{10} are independently

hydrogen;

straight or branched chain (C₁-C₆)alkyl;

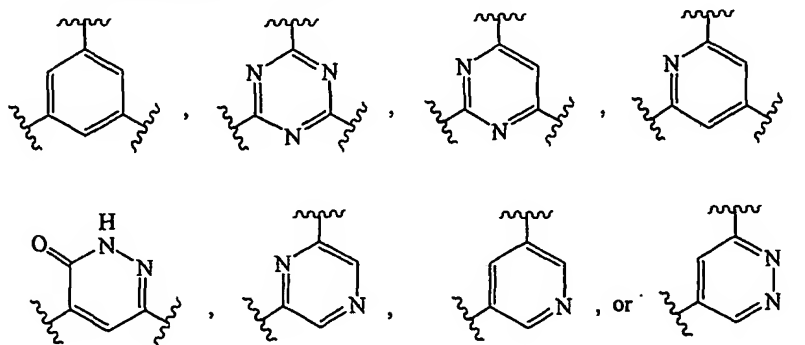
phenyl or benzyl which may each independently be

unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl; or

heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl;

[0012] each m is independently 0 or 1; and

[0013] W is a monocyclic ring having the structure



[0014] In another embodiment, a pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof and a pharmaceutically acceptable carrier.

[0015] In still another embodiment, a method of treating a kinase-implicated disorder in a mammal comprises administration to the mammal of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof and a pharmaceutically acceptable carrier.

[0016] In another embodiment, a method for identifying a kinase comprises contacting an organism, cell, or preparation comprising the kinase with a compound of Formula 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, and detecting modulation of the kinase activity.

DETAILED DESCRIPTION

[0017] The compounds of Formula 1 are novel compounds belonging to the family of aromatic monocycles, in particular amino-substituted aromatic monocycles. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula 1 with a kinase (i.e., one or more kinases) results in modulation of the activity of the kinase(s). The compounds of Formula 1 are thus expected to have therapeutic application in mammalian kinase-implicated conditions. As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of a compound of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may increase or decrease kinase activity by directly binding to the kinase, by causing (directly or indirectly) another factor to increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

[0018] The following definitions are used herein.

[0019] When any variable occurs more than one time in Formula 1, its definition on each occurrence is independent of its definition at every other occurrence.

[0020] By "heteroaryl" is meant systems, (as numbered from the linkage position assigned priority 1), such as 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolyl, 4-morpholinyl, piperidinyl, 4-piperazinyl, and the like.

[0021] By "heteroalkyl" is meant an aliphatic ring containing at least 1 carbon atom in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, or nitrogen.

[0022] By "sulfonamide" is meant $-S(O)_2NR-$ in either S-linked or N-linked orientation, where the nitrogen atom can be unsubstituted (i.e., R is hydrogen), mono- or disubstituted with cyclo-(C₃-C₆ alkyl)-methyl; or mono- or disubstituted with straight or branched chain C₁-C₆ alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member alkyl or heteroalkyl ring. By "piperazinyl" is meant unsubstituted piperazinyl, as well as piperazines independently substituted on 1-4 carbon atoms with hydroxy, cyano, amino, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, mono- or di((C₁-C₆)alkyl)amino(C₁-C₆)alkyl, or sulfonamide.

[0023] By "(C₁-C₆)alkyl" is meant straight or branched chain alkyl groups or cycloalkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred (C₁-C₆)alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl, cyclopropylmethyl, cyclohexyl, and the like. Similarly, by "(C₁-C₇)alkyl" is meant straight or branched chain alkyl groups or cycloalkyl groups having 1-7 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred (C₁-C₇)alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl, cyclopropylmethyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

[0024] By “(C₁-C₆)alkoxy” is meant an alkyl group of indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Preferred (C₁-C₆)alkoxy groups herein are (C₁-C₄)alkoxy groups.

[0025] By “alkylamino” is meant a group bonded via a secondary or tertiary nitrogen, while “aminoalkyl” means a group bonded via the alkyl group, the alkyl group containing a primary amino group.

[0026] The term “halogen” includes fluorine, chlorine, bromine, and iodine.

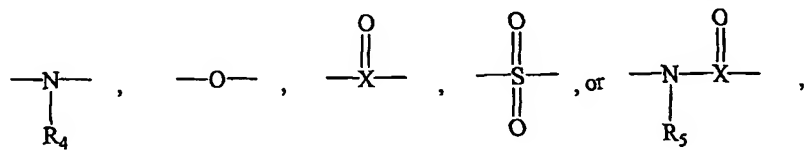
[0027] In a preferred embodiment, R₁, R₂, and R₃ are each independently

(C₁-C₆)alkoxy;

mono- or di((C₁-C₆)alkyl)amino, wherein the alkyl group may be unsubstituted, mono- di-, or tri-substituted with (C₁-C₇)alkoxy or phenoxy, and further wherein the phenoxy may be unsubstituted or substituted with hydroxy, nitro, cyano, amino, halogen, (C₁-C₆)alkyl, or (C₁-C₆)alkoxy;

phenyl, benzyl, or heteroaryl which may be unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, acetyl, phenyl which may be unsubstituted or substituted with one or more of (C₁-C₇)alkyl, (C₁-C₇)alkoxy, hydroxy, nitro, oxo, cyano, amino, or halogen, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, mono- or di((C₁-C₆)alkyl)amino(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkyl which may be unsubstituted or substituted with one or more of hydroxy, nitro, oxo, cyano, amino, or halogen, or heteroaryl which may be bonded through an ether, sulfide, or oxo group;

[0028] Also in a preferred embodiment, Z₁, Z₂ and Z₃ are each independently

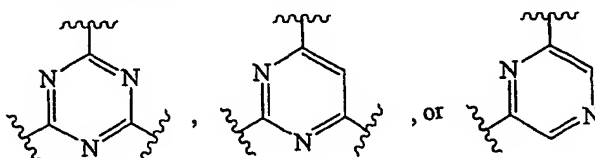


wherein

X is C; and

R_4 - R_5 are independently hydrogen; straight or branched chain (C_1 - C_6)alkyl; or phenyl which may be unsubstituted, mono-, di- or trisubstituted with one or more of phenyl, hydroxy, nitro, cyano, amino, or halogen.

[0029] Also in a preferred embodiment, W has the structure



[0030] In a particularly preferred embodiment, n is one; m is zero; Z is -NH-; and

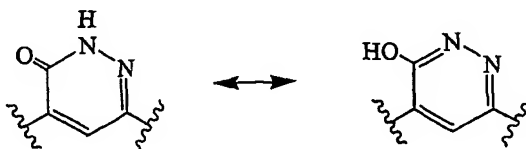
R_1 , R_2 , and R_3 are each independently

(C_1 - C_3)alkoxy; or

phenyl, benzyl, or heteroaryl which may be unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, acetyl, phenyl which may be unsubstituted or substituted with one or more of (C_1 - C_7)alkyl, (C_1 - C_7)alkoxy, hydroxy, nitro, oxo, cyano, amino, or halogen, (C_1 - C_6)alkoxy, (C_1 - C_6)alkyloxy(C_1 - C_6)alkoxy, mono- or di((C_1 - C_6)alkyl)amino, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkyl which may be unsubstituted or substituted with one or more of hydroxy, nitro, oxo, cyano, amino, or halogen, or heteroaryl which may be bonded through an ether, sulfide, or oxo group; or

phenoxyphenyl where each phenyl may be independently unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, halogen, (C_1 - C_6)alkyl, or (C_1 - C_6)alkoxy.

[0031] It will be understood that all tautomer forms of any W group are included, for example:



[0032] If the compounds of Formula 1 have asymmetric centers, then Formula 1 includes all of the optical isomers and mixtures thereof. In addition, compounds

with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. Where a compound of Formula 1 exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, and includes all tautomeric forms of the compound.

[0033] Representative compounds of the present invention, which are encompassed by Formula 1, include, but are not limited to their pharmaceutically acceptable acid addition salts. Non-toxic "pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, or nitrate salts; or salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0034] In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, it may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts encompassed by Formula 1.

[0035] The present invention also encompasses the prodrugs of the compounds of Formula 1, for example acylated prodrugs of the compounds of Formula 1. Those skilled in the art will recognize various synthetic methodologies

that may be used to prepare non-toxic pharmaceutically acceptable acylated and other prodrugs of the compounds encompassed by Formula 1.

[0036] Methods for obtaining the compounds described herein are known to those of ordinary skill in the art, suitable procedures being described, for example, in the references cited herein.

[0037] The present inventors have discovered new aromatic monocycles and determined that they are active as kinase inhibitors. The inhibitors of the present invention are expected to have therapeutic application in mammalian kinase-implicated conditions. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula 1 with various kinases results in the pharmaceutical utility of these compounds. Suitable kinases include but are not limited to tyrosine kinases and serine/threonine kinases, which may be classified as including the AGC group (cyclic nucleotide regulated family) of protein kinases, which includes the cyclic nucleotide regulated protein kinase family (e.g., PKA and PKG), the diacylglycerol-activated/phospholipid-dependent family protein kinase C family (e.g., PKC), the PKA and PKC-related family (e.g., RAC and Akt), the kinases that phosphorylate G protein-coupled receptors family, the budding yeast AGC-related protein kinase family, the kinases that phosphorylate ribosomal protein S6 family, the budding yeast DBF2/20 family, the flowering plant PVPK1 protein kinase homolog family, and other AGC related kinase families.

[0038] The CaMK (calcium calmodulin dependent) group of protein kinases includes kinases regulated by Ca^{2+} /CaM and close relatives family, the KIN1/SNF1/Nim1 family, and other related CaMK related kinase families. The CMGC group (named because it includes the cyclin-dependent kinases) includes the cyclin-dependent kinases (e.g., CDKs) and close relatives family, the ERK (e.g., MAP) kinase family, the glycogen synthase 3 (e.g., GSK3) family, the casein kinase II family, the Clk family and other CMGC kinases.

[0039] The PTK group of protein kinases includes protein-tyrosine kinases that may be nonmembrane-spanning or membrane-spanning tyrosine kinases. The PTK group of protein kinases includes the Src family, the Tek/Atk family, the Csk family, the Fes (Fps) family, the Abl family, the Syk/ZAP70 family, the Ttk/Jak1 family, the Ack family, the focal adhesion kinase (Fak) family, the epidermal growth

factor receptor family, the Eph/Elk/Eck receptor family, the Axl family, the Tie/Tek family, the platelet-derived growth factor receptor family, the fibroblast growth factor receptor family, the insulin receptor family, the LTK/ALK family, the Ros/Sevenless family, the Trk/Ror family, the DDR/TKT family, the hepatocyte growth factor receptor family, the nematode Kin15/16 family and other PTK kinase families.

[0040] The OPK group (other protein kinases) includes the Polo family, the MEK/STE7 family, the PAK/STE20 family, the MEKK/STE11 family, the NimA family, the wee1/mik1 family, the kinases involved in transcriptional control family, the Raf family, the Activin/TGF β receptor family, the flowering plant putative receptor kinases and close relatives family, the PSK/PTK leucine zipper domain family, the casein kinase I family, the PKN prokaryotic protein kinase family and other OPK protein kinase families. A large number of kinases are found in G. Hardie and S. Hanks, Eds., "Protein Kinase FactsBook", Academic Press (1995), ISBN 0-12-324719-5 (1995).

[0041] Accordingly, a method of treating a kinase-implicated disease or condition in a mammal, preferably a human, comprises administration to the mammal of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula 1 and a pharmaceutically acceptable carrier. The mammal is preferably a human, and may also be a companion animal, such as, for example, a dog or a cat, or a livestock animal. As used herein "therapeutically effective" includes alleviation of disease, disease symptoms, preventative, and prophylactic treatment.

[0042] Kinases are implicated in a large variety of diseases, as certain mutations in protein kinases can lead to activation of pathways causing, for example, the production of tumors, while other mutations in protein kinases block pathways and prevent a response. Some diseases that are linked to mutations in protein kinases are listed in the KinMutBase database (<http://www.uta.fi/imt/bioinfo/KinMutBase/>) (Stenberg et al., Nucleic Acids Research, Vol. 28, pp. 369-372, 2000). Diseases caused by protein kinase mutations include X-linked agammaglobulinemia (XLA), and non-insulin dependent diabetes mellitus (NIDDM), and severe combined immunodeficiency (SCID). Mutations related to tumor development have been linked to such diseases as Hirschprung's disease, multiple endocrine neoplasia type 2

(MEN2) a and b, medullary thyroid carcinoma (FMTTC), papillary renal carcinoma (HPRC), and Peutz-Jeghers syndrome.

[0043] Mutations in growth factor receptor kinases are linked to diseases such as mastocytosis, systemic mast cell disease, piebaldism, hypochondroplasia, thanatophoric dysplasia, and skeletal dysplasia. Other protein kinase-linked diseases include Coffin-Lowry syndrome, congenital insensitivity to pain with anhidrosis (CIPA), hypertension, vascular dysplasia, errors in vascular morphogenesis, and X-linked mental retardation. Mutations in protein kinases have also been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD).

[0044] Other diseases associated with protein kinases include Gaucher disease, hypochromic anemia, granulomatous disease, ataxia-telangiectasia, familial hypercholesterolemia, certain types of muscular dystrophy such as Driefuss-Emory type, cystic fibrosis, type 1 hyperlipoproteinemia, Treacher Collins Franceschetti syndrome 1, Tay-Sachs disease, type 1 neurofibromatosis, adenomatous polyposis of the colon, X-linked ichthyosis, and Beckwith-Weidemann Syndrome.

[0045] Altered PKA (cyclic AMP-dependent protein kinase) expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease. Altered MAP (mitogen-activated protein) kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development. RTKs (receptor tyrosine kinases), CDKs and STKs (serine/threonine kinases) have all been implicated in a host of pathogenic conditions including, significantly, large number of diverse cancers. Other pathogenic conditions that have been associated with PTKs include psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restinosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune disease, and a variety of renal disorders.

[0046] Preferably, the conditions, diseases and/or disorders that can be affected using compounds and compositions according to the invention include, but are not limited to, psoriasis, cancer (for example, chronic myelogenous leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, breast cancer, ovarian

cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

[0047] The invention also provides pharmaceutical compositions comprising at least one compound of the invention together with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. Such pharmaceutical compositions include packaged pharmaceutical compositions for treating disorders responsive to modulation of kinase activity. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one kinase modulator as described supra and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a disorder responsive to kinase modulation in the patient. Those skilled in the art will also recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

[0048] The compounds of general Formula 1 may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. The pharmaceutical compositions containing compounds of general Formula 1 may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0049] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order

to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[0050] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0051] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0052] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0053] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring, and coloring agents, may also be present.

[0054] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

[0055] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium

chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0056] The compounds of general Formula 1 may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0057] Compounds of general Formula 1 may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives, and buffering agents can be dissolved in the vehicle.

[0058] For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

[0059] Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0060] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of eating disorders, including obesity, a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of impotence a single dose that rapidly reaches effective concentrations is desirable.

[0061] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0062] Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding, and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

[0063] Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

[0064] Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* 1996, volume 677, pages 1-27).

[0065] Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* 1998, volume 26, pages 1120-1127).

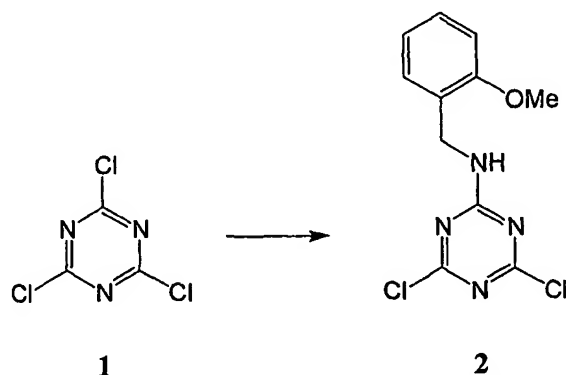
[0066] In another embodiment, the compounds of Formula 1 are also useful as probes for the localization of kinases of therapeutic interest, that is, for both *in vivo* and *in vitro* identification and isolation the specific proteins to which it binds.

[0067] In another embodiment, the compounds of Formula 1 are also useful as probes for the localization of kinases of therapeutic interest, that is, for both *in vivo* and *in vitro* identification and isolation the specific proteins to which it binds. A method for identifying a kinase comprises contacting an organism, cell, or preparation comprising the kinase with compound or salt according to Formulas 1, 2, or 3, and

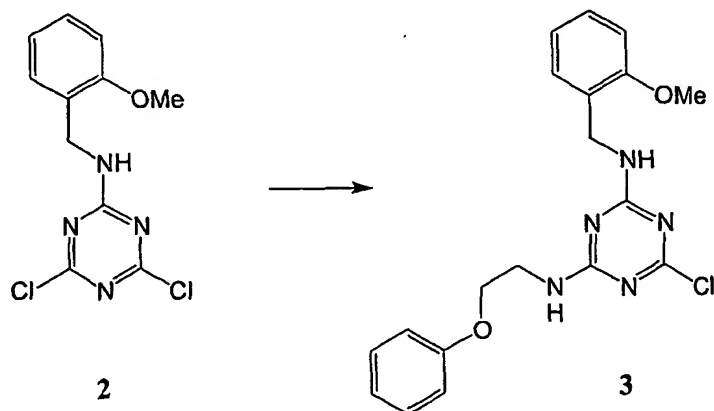
detecting modulation of an activity of the kinase. Suitable methods for detecting kinase modulation are known, for example those described herein.

[0068] The invention is further illustrated by the following non-limiting examples.

Example 1. Representative synthesis of compounds of Formula 1.



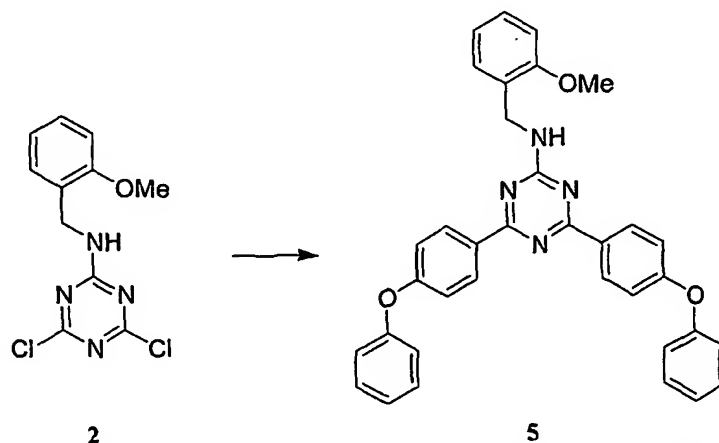
[0069] (4,6-Dichloro-[1,3,5]triazin-2-yl)-(2-methoxybenzyl)-amine (2). A solution of 1.00 equivalents (eq.) of 2,4,6-trichloro-[1,3,5]triazine **1** in acetonitrile is cooled to 0°C under nitrogen and 1.10 eq. of NaHCO₃ solid is added. While maintaining internal temperature <5°C, 2-methoxybenzyl amine is added dropwise to the stirring suspension. After the reaction temperature drops back down to 0°C, stirring is continued for 30 minutes. The resulting white slurry is filtered and washed with H₂O several times, then washed sparingly with ethyl acetate and the resultant white solid **2** is dried under vacuum overnight.



[0070] 6-Chloro-N-(2-methoxybenzyl)-N'-(2-phenoxyethyl)-[1,3,5]triazine-2,4-diamine (3). Procedure 1: 1.00 eq. of **2** in CH₂Cl₂ is cooled to 0°C under

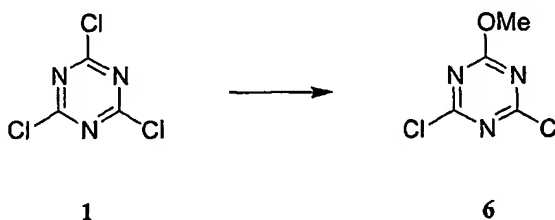
nitrogen and Et₃N or Hunig's base (3.00 eq.) is added. To the stirring solution, 1.00 eq. of 2-phenoxy-ethylamine is added dropwise. The temperature rises several degrees upon completion of addition; warming is then allowed to continue until the reaction reaches room temperature. The reaction is allowed to stir at room temperature for 12 hours and then the mixture is partitioned between CH₂Cl₂ and 1.0 N HCl. The acid layer is extracted once with CH₂Cl₂ and then the pooled CH₂Cl₂ layers washed several times with H₂O and once with brine. The CH₂Cl₂ extract is dried over Na₂SO₄, and the solvent removed under reduced pressure to provide crude 3, which is purified by flash chromatography using 1:4 ethyl acetate (EtOAc)/hexanes as eluent.

[0071] Procedure 2: 1.00 eq. of 2 in CH₂Cl₂ is cooled to 0°C under nitrogen and Et₃N or Hunig's base (3.00 eq.) is added. To the stirring solution, 1.00 eq. of 2-phenoxy-ethylamine is added dropwise. The temperature rises several degrees upon completion of addition; warming is then allowed to continue until the reaction reaches room temperature. The resulting mixture is heated to 100°C for 30 minutes, cooled to room temperature, and partitioned between H₂O/CH₂Cl₂. The aqueous layer is extracted with CH₂Cl₂ and combined organic extracts were dried over Na₂SO₄. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1:4 EtOAc/hexanes) to yield 3.

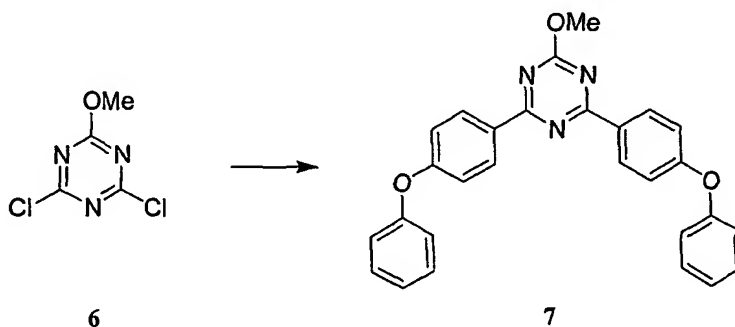


[0072] [4,6-Bis-(4-phenoxyphenyl)-[1,3,5]triazin-2-yl]-(2-methoxy-benzyl)-amine (5). A solution of 1.00 eq. of 2 in 1 mL toluene is treated with 10-mole percent tetrakis(triphenylphosphine) palladium under nitrogen at room temperature. To

this solution is added directly 3.00 eq. of 4-phenoxyphenyl boronic acid and then 1 mL Na_2CO_3 (1.0 M, 6 eq.) solution. The reaction vial is capped and the reaction is stirred under nitrogen at 90°C for 10 hours. The toluene layer is separated and removed under reduced pressure, and the resulting oil is purified via flash chromatography to provide 5.

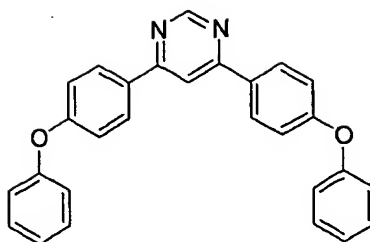


[0073] 2,4-Dichloro-6-methoxy-[1,3,5]triazine (6) 1.00 Eq. of 2,4,6-trichloro-[1,3,5]triazine is dissolved in methanol with heating, cooled to room temperature and solid NaHCO_3 (2.50 eq.) is added portion wise. After gas evolution ceases (approximately 30 minutes), water is added and the remaining white solid filtered. Compound 6 is carried forward without further purification.



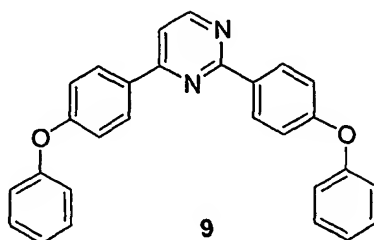
[0074] 2-Methoxy-4,6-bis-(4-phenoxyphenyl)-[1,3,5]triazine (7). A solution of 1.00 eq. of 2 in 1 mL toluene is treated with 10 mole percent tetrakis(triphenylphosphine) palladium under nitrogen at room temperature. To this solution is added directly 3.00 eq. of 4-phenoxyphenyl boronic acid and then 1 mL Na_2CO_3 (1.0 M, 6 eq.) solution. The reaction vial is capped and the reaction is stirred under nitrogen at 90°C for 10 hours. The toluene layer is separated and removed under reduced pressure, and the resulting oil is purified via flash chromatography to provide 7.

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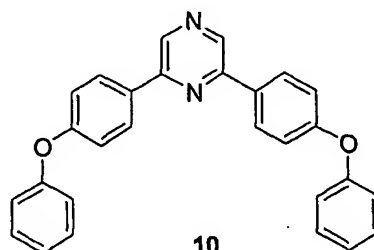
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[0075] 4,6-Bis-(4-phenoxy-phenyl)-pyrimidine (8) is prepared from 4,6-dichloro-pyrimidine as described for 7.



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[0076] 2,4-Bis-(4-phenoxy-phenyl)-pyrimidine (9) is prepared from 2,4-dichloro-pyrimidine using method described for 7.



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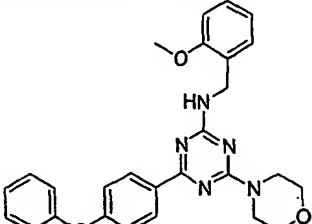
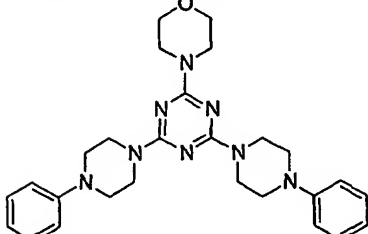
[0077] 2,6-Bis-(4-phenoxy-phenyl)-pyrazine (10) is prepared from 2,6-dichloropyrazine using method described for 7.

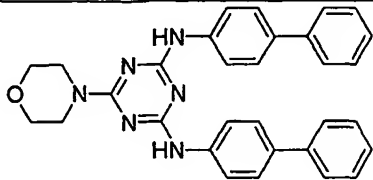
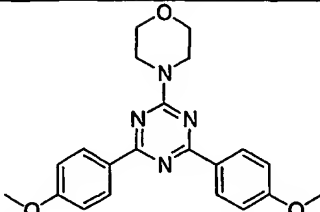
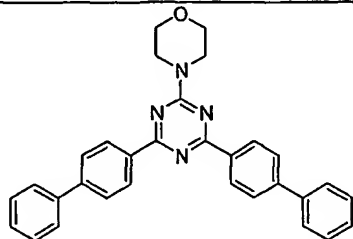
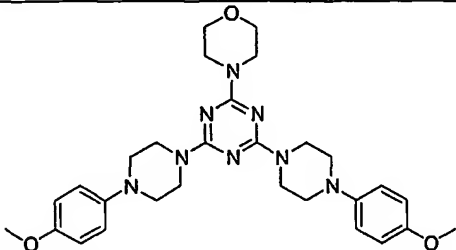
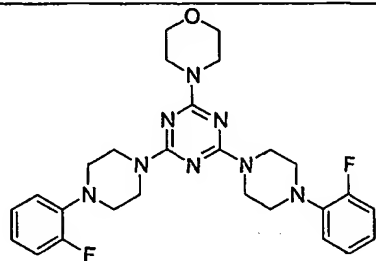
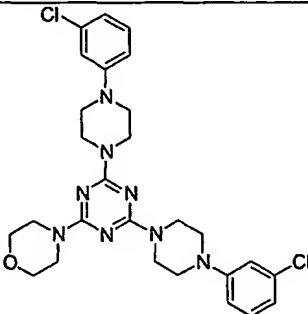
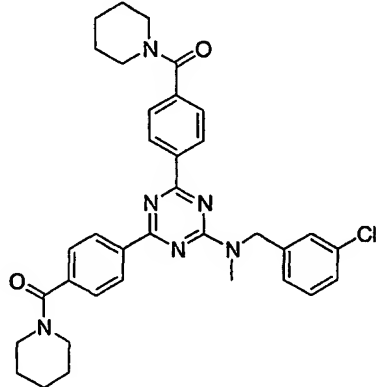
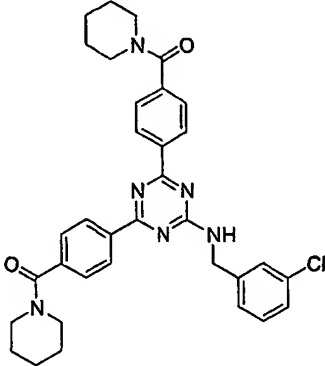
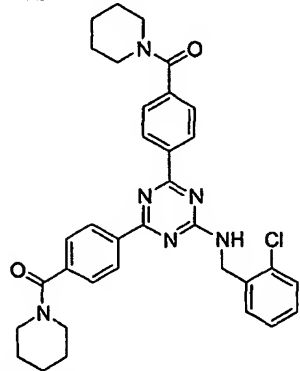
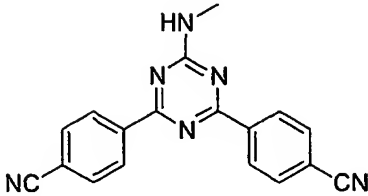
Example 2: The following compounds were using the procedures described in Example 1. Structures are shown in the Table.

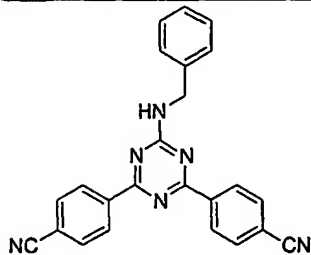
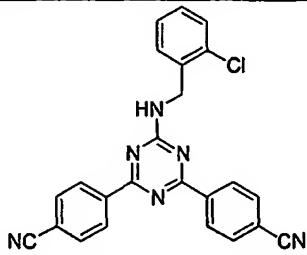
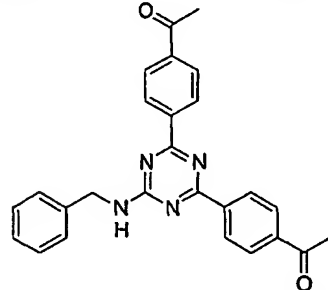
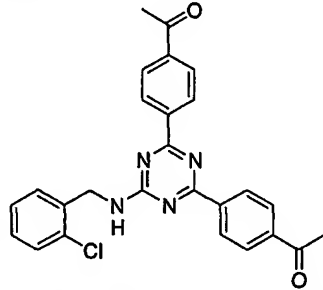
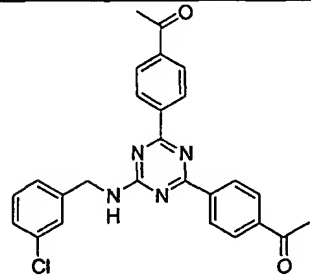
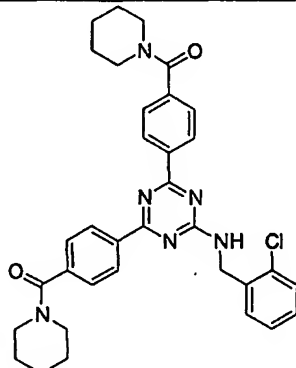
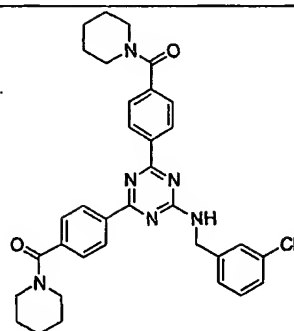
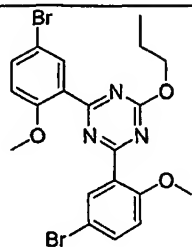
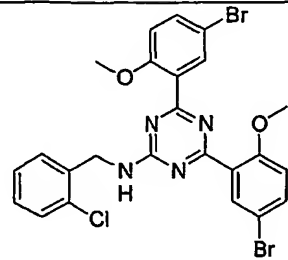
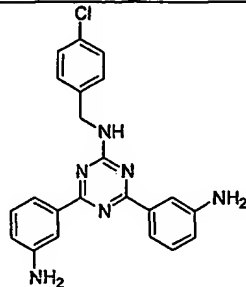
- (a) (2-Methoxybenzyl)-[4-morpholin-4-yl-6-(4-phenoxyphenyl)-[1,3,5]triazin-2-yl]-amine, $\text{MF}=\text{C}_{27}\text{H}_{27}\text{N}_5\text{O}_3$, $\text{MW}=469.54$ Mass Spec m/z ($\text{M}^+ + 1$) 470.22.
- (b) 2-Morpholin-4-yl-4,6-bis-(4-phenylpiperazin-1-yl)-[1,3,5]triazine, $\text{MF}=\text{C}_{27}\text{H}_{34}\text{N}_8\text{O}$, $\text{MW}=486.61$ Mass Spec m/z ($\text{M}^+ + 1$) 487.30.

- (c) N,N'-Bis-biphenyl-4-yl-6-morpholin-4-yl-[1,3,5]triazine-2,4-diamine, MF=C₃₁H₂₈N₆O, MW=500.59, Mass Spec m/z (M⁺ +1) 501.27.
- (d) 2,4-Bis-(4-methoxyphenyl)-6-morpholin-4-yl-[1,3,5]triazine, MF=C₂₁H₂₂N₄O₃, MW=378.42, Mass Spec m/z (M⁺ +1) 379.15.
- (e) 2,4-Bis-biphenyl-4-yl-6-morpholin-4-yl-[1,3,5]triazine, MF=C₃₁H₂₆N₄O, MW=470.56, Mass Spec m/z (M⁺ +1) 471.25.
- (f) 2,4-Bis-[4-(4-methoxyphenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine, MF=C₂₉H₃₈N₈O₃, MW=546.66, Mass Spec m/z (M⁺ +1) 547.30.
- (g) 2,4-Bis-[4-(2-fluorophenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine, MF=C₂₇H₃₂F₂N₈O, MW=522.59, Mass Spec m/z (M⁺ +1) 523.26.
- (h) 2,4-Bis-[4-(3-chlorophenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine, MF=C₂₇H₃₂Cl₂N₈O, MW=555.50, Mass Spec m/z (M⁺ +1) 555.22.
- (i) (4-{4-[(3-Chlorobenzyl)-methyl-amino]-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone, MF=C₃₅H₃₇ClN₆O₂, MW=609.16, Mass Spec m/z (M⁺ +1) 609.27.
- (j) (4-{4-(3-Chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone, MF=C₃₄H₃₅ClN₆O₂, MW=595.13, Mass Spec m/z (M⁺ +1) 595.29.
- (k) (4-{4-(2-Chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone, MF=C₃₄H₃₅ClN₆O₂, MW=595.13, Mass Spec m/z (M⁺ +1) 595.28.
- (l) (4,6-Di-4-cyanophenyl-[1,3,5]triazin-2-yl)-methyl-amine, MF=C₁₈H₁₂N₆, MW=312.33, Mass Spec m/z (M⁺ +1) 313.02.
- (m) Benzyl-(4,6-di-4-cyanophenyl-[1,3,5]triazin-2-yl)-amine, MF=C₂₄H₁₆N₆, MW=388.42, Mass Spec m/z (M⁺ +1) 389.02.
- (n) (2-Chlorobenzyl)-(4,6-di-4-cyanophenyl-[1,3,5]triazin-2-yl)-amine, MF=C₂₄H₁₅ClN₆, MW=422.87, Mass Spec m/z (M⁺ +1) 422.98.

- (o) 1-{4-[4-(4-acetylphenyl)-6-benzylamino-[1,3,5]triazin-2-yl]-phenyl}-ethanone, MF=C₂₆H₂₂N₄O₂, MW=422.48, Mass Spec m/z (M⁺ +1) 423.03.
- (p) 1-{4-[4-(4-Acetyl-phenyl)-6-(2-chloro-benzylamino)-[1,3,5]triazin-2-yl]-phenyl}-ethanone, MF=C₂₆H₂₁ClN₄O₂, MW=456.92, Mass Spec m/z (M⁺ +1) 456.99.
- (q) 1-{4-[4-(4-Acetylphenyl)-6-(3-chlorobenzylamino)-[1,3,5]triazin-2-yl]-phenyl}-ethanone, MF=C₂₆H₂₁ClN₄O₂, MW=456.92, Mass Spec m/z (M⁺ +1) 456.99.
- (r) (4-{4-(2-Chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone, MF=C₃₄H₃₅ClN₆O₂, MW=595.13, Mass Spec m/z (M⁺ +1) 595.04.
- (s) (4-{4-(3-Chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone, MF=C₃₄H₃₅ClN₆O₂, MW=595.13, Mass Spec m/z (M⁺ +1) 595.05.
- (t) 2,4-Bis-(5-bromo-2-methoxyphenyl)-6-propoxy-[1,3,5]triazine, MF=C₂₀H₁₉Br₂N₃O₃, MW=509.19, Mass Spec m/z (M⁺ +1) 507.78.
- (u) [4,6-Bis-(5-bromo-2-methoxyphenyl)-[1,3,5]triazin-2-yl]-(2-chlorobenzyl)-amine, MF=C₂₄H₁₉Br₂ClN₄O₂, MW=590.69, Mass Spec m/z (M⁺ +1) 588.70.
- (v) [4,6-Bis-(3-amino-phenyl)-[1,3,5]triazin-2-yl]-(4-chlorobenzyl)-amine, MF=C₂₂H₁₉ClN₆, MW=402.88, Mass Spec m/z (M⁺ +1) 402.98.

Reference and Compound	Reference and Compound
<p>a</p> 	<p>b</p> 

Reference and Compound		Reference and Compound	
c		d	
e		f	
g		h	
i		j	
k		l	

Reference and Compound		Reference and Compound	
m		n	
o		p	
q		r	
s		t	
u		v	

Example 3. Generalized description a standard AKT-1 Kinase assay used herein.

[0078] In a final reaction volume of 40 μ l, active recombinant N-terminus his-tagged AKT-1/PKB \square kinase expressed in Sf21 cells (UBI # 14-276; 50-100 ng; 19-38 nM; about 4.5-9 mU) was incubated in 25 mM Tris pH 7.6; 5 mM Beta-glycerophosphate; 2 mM DTT; 100 μ M sodium vanadate; 10 mM MgCl_2 in 96-well Pierce Reacti-BindTM streptavidin-coated high binding capacity coated white plate (Pierce # 15502) coated with saturating amounts of biotinylated Crosstide peptide (UBI #12-385; biotin-KGSGSGRPRTSSFAEG; 50 pmoles; about 1.25 μ M) and initiated with the addition of 2.5 μ Ci ^{32}P - \square ATP (specific activity 3000 Ci/mmol; 10 mCi/ml; about 21 nM). Compounds were tested initially in duplicate wells for determination of initial IC_{50} inhibition in half log serial dilutions starting at 100 μ M with a final concentration of 2% DMSO. Following a 30 min incubation at 30°C, the reaction was stopped by aspiration and 4 x 100 μ l washes with TBS plus 0.05% Tween-20 prior to addition of 100 μ l scintillant and counting in Beckman TopCount instrument. Percent inhibition was calculated as $[1 - ((\text{AVE CPM}_{\text{compound}} - \text{AVE CPM}_{\text{no peptide background}}) / (\text{AVE CPM}_{\text{no compound MAX}} - \text{AVE CPM}_{\text{no peptide background}}))] * 100$. Staurosporine, a general ATP competitive kinase inhibitor was used as a reference compound and showed an IC_{50} of approximately 60-100 nM for AKT-1 in the current assay format. Approximate S/N ratios are 8-12X with AVE CPM of Maximum about 15k and no peptide background about 1.5 K. Improved S/N ratios can be obtained using higher amounts of either AKT-1 kinase or ^{32}P - \square ATP. Cold ATP was not added in current format but has been added at up to 200 μ M in the presence of 5 μ Ci ^{32}P - \square ATP resulting in S/N ratios of approximately 5-10X.

Example 4. Generalized description of a standard AKT-1 Kinase assay.

[0079] A generalized description the standard assay to evaluate modulation of cell growth in soft agar (using cell lines HCT-15 (colon cancer), MiaPaca2 (pancreatic cancer), MCF-7 (breast cancer) and a NIH3T3 clone stably over-expressing transfected myrAkt-1 human gene, for example) is as follows.

[0080] Preparation of the agar base layer: A quantity of 500 ml of 2X DMEM (phenol red free, Sigma Cat # D2902) is prepared, and sterile filtered. To that solution is added 10 ml of sodium pyruvate (Gibco, Cat # 11360-070), 10 ml of

penicillin/streptomycin (Gibco, Cat# 15140-122), 10 ml of Glutamax (Gibco, cat# 33050-061) and 100 ml of heat-inactivated FBS (Gemini) to make 2X DMEM complete media stock. Two stock concentrations of Sea Plaque low melt agar (Biowhittaker, Cat # 431097), 1%, and 0.6%, are prepared with ultra pure milliQ water, and sterilized by autoclaving. To prepare the agar base layer for a 12-well plate (Falcon # 353042), 6 ml of the 2X DMEM stock is mixed with 6 ml of 1% agar stock, both at 37°C, and 1 ml of the resulting mixture is added to each well of the 12 well plate, 3 hrs prior to setup of top layer.

[0081] Top layer with cells and compound for evaluation: Cells at 60-80% confluency (log growth) in T75 are trypsinized with 1 ml of 1x trypsin solution (Gibco), neutralized with 10 ml of 1x DMEM 10% FBS and viable cells counted using a hemocytometer via trypan blue exclusion. A working stock of 2.5×10^4 cells / ml is prepared in 1x DMEM 10% FBS. A 15 ml centrifuge tube is prepared for each concentration of compound tested in duplicate wells of a 12 well plate. The following are added in order: 1 ml of 2X DMEM stock at 37°C; compound at 2X final desired concentration (using 4 microliter volume from a 1000X concentrated dilution series in 100 % DMSO); followed by 2,500 cells (using 100 microliters of 1×10^4 cell /ml working stock), and finally 1 ml of 0.6 % agar stock at 37°C. Following careful mixing, 1 ml each is added to duplicate wells of the 12-well plate. The plate is then placed in a 37°C, 5% CO₂, humidified incubator for 10 to 14 days and read. Rapid diffusion of CPD throughout top and bottom agar layer results in final drug concentration of 1X.

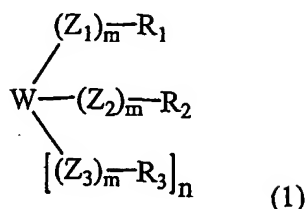
[0082] Counting Colonies: After 10 days of incubation, the plates are removed from the incubator for photography and colony counting. Each well is scanned using an eyepiece with a micrometer guide and 5x phase optics. Colonies 50 micrometer or greater in diameter are scored as positive. Duplicate wells are averaged and percent inhibition calculated using number of colonies in no compound control wells as 100%.

[0083] All compounds described in Examples 1 and 2 were tested according to the above protocols in examples 3 and 4 and determined to exhibit an IC₅₀ value less than or equal to 25 micromolar.

[0084] All cited references are incorporated herein in their entirety. While preferred embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations.

[0085] What is claimed is:

1. A compound having Formula 1:



5 a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein one or two of R_1 , R_2 , and R_3 may each independently be hydrogen; straight or branched chain (C_1-C_7) alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl ring; (cyclo (C_3-C_6) alkyl)methyl; (C_1-C_6) alkoxy; (C_1-C_6) alkyloxy (C_1-C_6) alkoxy; or
 10 sulfonamide, and

R_1 , R_2 , and R_3 may each independently be

mono- or di $((C_1-C_6)$ alkyl)amino, wherein the alkyl group may be unsubstituted, mono- di-, or tri-substituted with phenyl, (C_1-C_7) alkoxy or phenoxy, further wherein the phenyl and/or phenoxy may be unsubstituted or
 15 substituted with hydroxy, nitro, cyano, amino, halogen, straight or branched chain (C_1-C_7) alkyl or (C_1-C_6) alkoxy;

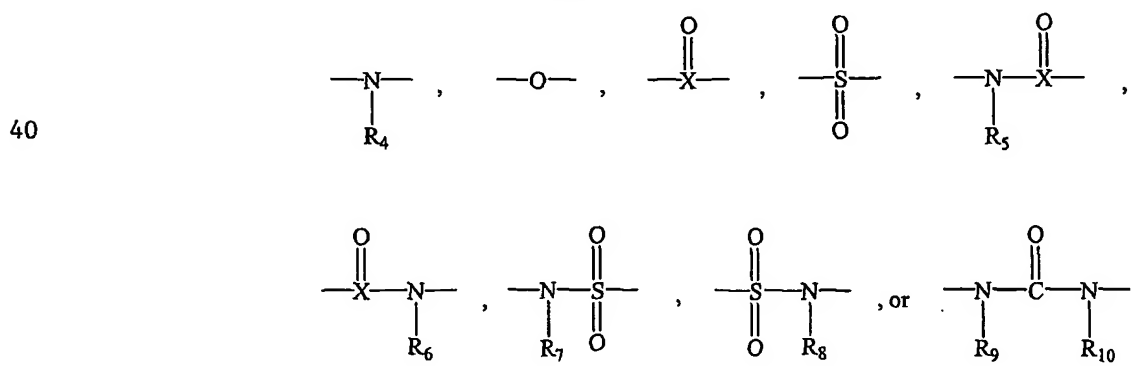
phenyl, benzyl, or heteroaryl which may be unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, acetyl, phenyl which may be unsubstituted or substituted with one or more of
 20 (C_1-C_7) alkyl, (C_1-C_7) alkoxy, hydroxy, nitro, oxo, cyano, amino, or halogen, (C_1-C_6) alkoxy, (C_1-C_6) alkyloxy (C_1-C_6) alkoxy, mono- or di $((C_1-C_6)$ alkyl)amino, mono- or di $((C_1-C_6)$ alkyl)amino (C_1-C_6) alkyl, amino (C_1-C_6) alkyl, (C_1-C_6) alkyl which may be unsubstituted or substituted with one or more of hydroxy, nitro, oxo, cyano, amino, or halogen, or heteroaryl which
 25 may be bonded through an ether, sulfide, or oxo group;

heteroaryloxy or phenoxyphenyl where each heteroaryl or phenyl may be independently unsubstituted, mono-, di-, or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkyloxy (C_1-C_6) alkoxy, mono- or di $((C_1-C_6)$ alkyl)amino,
 30 or amino (C_1-C_6) alkyl;

4-phenyl- or 4-heteroaryl-1-piperazinyl where the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, mono- or di((C₁-C₆)alkyl)amino(C₁-C₆)alkyl);

n is 0 or 1;

Z₁, Z₂ and Z₃ are each independently



wherein

45 X is C or S; and

R₄-R₁₀ are independently

hydrogen;

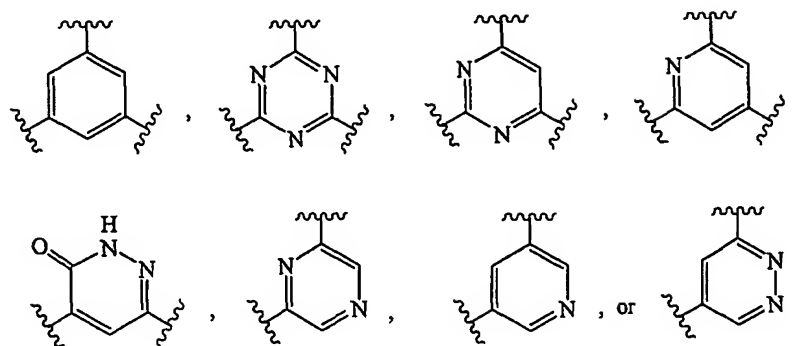
straight or branched chain (C₁-C₆)alkyl;

phenyl or benzyl which may each independently be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl; or

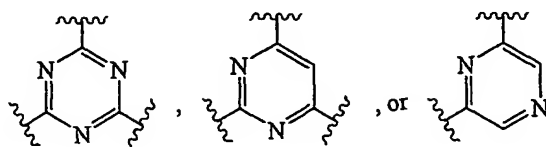
heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyloxy-(C₁-C₆)alkoxy, mono- or di((C₁-C₆)alkyl)amino, amino(C₁-C₆)alkyl;

each m is independently 0 or 1; and

W is a monocyclic ring having the structure



2. The compound or salt according to claim 1, wherein W has the structure



3. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (2-methoxybenzyl)-[4-morpholin-4-yl-6-(4-phenoxyphenyl)-[1,3,5]triazin-2-yl]-amine.

4. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2-morpholin-4-yl-4,6-bis-(4-phenyl-piperazin-1-yl)-[1,3,5]triazine.

5. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is N,N'-bis-biphenyl-4-yl-6-morpholin-4-yl-[1,3,5]triazine-2,4-diamine.

6. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-(4-methoxyphenyl)-6-morpholin-4-yl-[1,3,5]triazine.

7. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-biphenyl-4-yl-6-morpholin-4-yl-[1,3,5]triazine.

8. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-[4-(4-methoxyphenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine.

9. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-[4-(2-fluorophenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine.

10. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-[4-(3-chlorophenyl)-piperazin-1-yl]-6-morpholin-4-yl-[1,3,5]triazine.

11. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4-{4-[(3-chlorobenzyl)-methyl-amino]-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone.

12. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4-{4-(3-chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone.

13. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4-{4-(2-chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone.

14. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4,6-di-p-cyano-[1,3,5]triazin-2-yl)-methylanine.

15. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is benzyl-(4,6-di-p-cyano-[1,3,5]triazin-2-yl)-amine.

16. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (2-chlorobenzyl)-(4,6-di-p-cyano-[1,3,5]triazin-2-yl)-amine.

17. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 1-{4-[4-(4-acetylphenyl)-6-benzylamino-[1,3,5]triazin-2-yl]-phenyl}-ethanone.

18. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 1-{4-[4-(4-acetylphenyl)-6-(2-chloro-benzylamino)-[1,3,5]triazin-2-yl]-phenyl}-ethanone.

19. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[4-(4-acetylphenyl)-6-(3-chlorobenzylamino)-[1,3,5]triazin-2-yl]-phenyl}-ethanone.

20. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4-{4-(2-chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone.

21. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is (4-{4-(3-chlorobenzylamino)-6-[4-(piperidine-1-carbonyl)-phenyl]-[1,3,5]triazin-2-yl}-phenyl)-piperidin-1-yl-methanone.

22. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is 2,4-bis-(5-bromo-2-methoxy-phenyl)-6-propoxy-[1,3,5]triazine.

23. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is [4,6-Bis-(5-bromo-2-methoxyphenyl)-[1,3,5]triazin-2-yl]-(2-chloro-benzyl)-amine.

24. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein the compound is [4,6-bis-(3-amino-phenyl)-[1,3,5]triazin-2-yl]-(4-chloro-benzyl)-amine.

25. A compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein in an in vitro assay of kinase modulation, the compound exhibits a IC_{50} value less than or equal to 25 micromolar.

26. A pharmaceutical composition comprising
a compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof, and
at least one pharmaceutically acceptable carrier or excipient.

27. A method of treating a kinase-implicated condition in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, prodrug, or mixture thereof.

28. The method of claim 27 wherein the mammal is a human.

29. The method of claim 27 wherein the mammal is a dog or cat.

30. The method of claim 27 wherein the mammal is a livestock animal.

31. A method for identifying a kinase, comprising
contacting an organism, cell, or preparation comprising the kinase with a
compound as in claim 1, a pharmaceutically acceptable salt, hydrate, solvate, crystal
form, diastereomer, prodrug, or mixture thereof; and

5 detecting modulation of an activity of the kinase.

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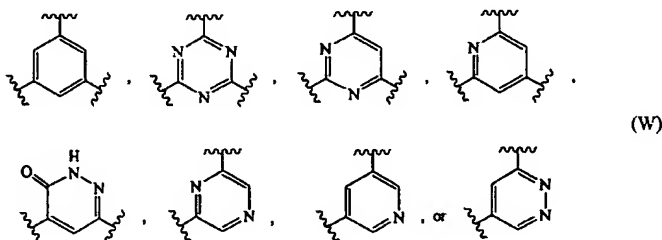
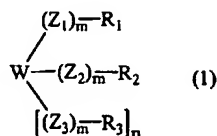
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(54) Title: CERTAIN AROMATIC MONOCYCLES AS KINASE MODULATORS



(57) Abstract: Compound having Formula (I): wherein (W) is a monocyclic ring having the structure are useful as modulators of kinase activity.

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

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Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/025220 A (ARMISTEAD DAVID M ;DIPIETRO LUCIAN V (US); GEUNS MEYER STEPHANIE D) 12 April 2001 (2001-04-12) cited in the application page 33, line 17 - page 34, line 11	1,2, 25-31
Y	claim 1, examples	3-24
X	WO 01/047921 A (LETOURNEAU JEFFREY JOHN ;RIVIELLO CHRISTOPHER MARK (US); INGLESE J) 5 July 2001 (2001-07-05) claims 1,11-14 examples	1,2, 25-31
X	WO 01/047897 A (SQUIBB BRISTOL MYERS CO ;PHARMACOEPIA INC (US)) 5 July 2001 (2001-07-05)	1,2, 25-31
Y	claims 1,28,29 examples	3-24
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☒ Patent family members are listed in annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search

19 September 2003

Date of mailing of the International search report

21.01.04

Name and mailing address of the ISA

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Authorized officer

Seymour, L

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/US 03/19961

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	W0 00/78738 A (PARKER HUGHES INST) 28 December 2000 (2000-12-28)	1,2, 25-31
Y	claims 1,19-21 examples -----	3-24
X	EP 0 563 386 A (NIPPON SHINYAKU CO LTD) 6 October 1993 (1993-10-06)	1,2, 25-31
Y	claims 1-3 -----	3-24
X	W0 99/31088 A (ABBOTT LAB) 24 June 1999 (1999-06-24)	1,2, 25-31
Y	page 10, line 6 - page 11, line 19 claim 1, examples -----	3-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/19961

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2(part);3-24;25-31(part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,2(part); 3-24; 25-31(part)

Compounds of formula (1) wherein W is a triazine moiety and corresponding compositions and uses

2. claims: 1; 25-31(part)

Compounds of formula (1) wherein W is a phenyl moiety and corresponding compositions and uses

3. claims: 1,2(part); 25-31(part)

Compounds of formula (1) wherein W is a pyrimidine moiety and corresponding compositions and uses

4. claims: 1(part); 25-31(part)

Compounds of formula (1) wherein W is a pyridine moiety and corresponding compositions and uses

5. claims: 1(part); 25-31(part)

Compounds of formula (1) wherein W is a pyridazine moiety and corresponding compositions and uses

6. claims: 1,2(part); 25-31(part)

Compounds of formula (1) wherein W is a pyrazine moiety and corresponding compositions and uses

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

The initial phase of the search for the first invention revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds as recited in claims 3-24.

In addition the present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include prodrugs of the claimed compounds.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 03/19961

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